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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,368	10/26/2001	James P. Hoefler	IVGN 274.2 DIV	2504
53050 7590 12/23/2008 INVITROGEN CORPORATION C/O INTELLEVATE P.O. BOX 52050 MINNEAPOLIS, MN 55402				
EXAMINER				
COOK, LISA V				
ART UNIT		PAPER NUMBER		
1641				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/035,368

**Applicant(s)**

HOEFFLER ET AL.

**Examiner**

LISA V. COOK

**Art Unit**

1641

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 15 December 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 18, 71-82, 84 and 88-92 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 18, 71-82, 84 and 88-92 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/15/08 has been entered.

### ***Claim Status***

2. Applicants' response to the Office Action mailed 5/18/07 is acknowledged (Paper filed 11/19/07). In the amendment filed therein claim 18 was modified. Claims 1-17, 19-70, 83, and 85-87 have been canceled. New claims 88-92 have been added. Currently, claims 18, 71-82, 84 and 88-92 are pending and under consideration.

3. Rejections and/or objections of record not reiterated below have been withdrawn.

## NEW GROUNDS OF REJECTIONS NECESSITATED BY AMENDMENT

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 18 and 90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims have been amended to recite antibodies coupled to a surface, however support for this limitation is not found in the disclosure. Page 17 section 0067 merely teaches coupling of an antigen to a label. Antibodies coupled to a surface are not found in the specification. Applicant is invited to show support for the newly submitted claim language.

### ***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 18, 71, and 88-92 are rejected under 35 U.S.C. 103(a) as being obvious over Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) in view of Bernard Blanc (Bulletin de la Societe de Chimie Biologique, 1959, Vol.41, 891-899, English Abstract) and further in view of Chu et al. (ACS Symposium Series, 1997, 657 (Immunochemical Technology for Environmental Applications, pages 170-184), Abstract Only.

Unla et al. teach assay procedures to detect protein differences between two samples. The protein differences between two samples are evaluated in a modified 2-DE (two dimensional polyacrylamide gel electrophoresis) technique called difference gel electrophoresis (DIGE). In particular, two protein samples are labeled with two cyanine dyes. This allows for the simultaneous measurement of both samples on the same gel. Differences in the two samples due to differences in gene expression or protein modification can be identified quickly. See page 2071, 2<sup>nd</sup> column .

In one embodiment *E. coli* transformed with the chimeric protein GAL4VP16 were induced for 15 min with IPTG. Extracts (Applicant's cell extracts) were labeled with either Cy3 or Cy5 and compared. See figure 4 on page 2076, for example.

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Unla et al. are silent with respect to antibody utility in their two dimensional electrophoresis procedures.

However, Bernard Blanc teaches that the technique of 2-dimensional immunoelectrophoresis involves two consecutive electrophoresis at right angles followed by diffusion of specific antibodies in a gelatin medium. This process make it possible to better separate antigen-antibody precipitation arcs and thus allows for an easier differentiation of the corresponding constituents.

The method was evaluated in normal human serum and led to better differentiation in the zones of  $\alpha_2$ -,  $\beta_2$ -, and  $\gamma$ -globulins. Moreover, the procedure offers the advantage of allowing the combination of several other interesting techniques and makes possible a change of conditions between the first and the second electrophoresis. It, thus, becomes a method of interest in the study of complex protein mixtures, such as different biological fluids. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use antibodies in electrophoresis procedures as taught by Bernard Blanc in the 2D electrophoresis method of Unla et al. because Bernard Blanc taught that 2D electrophoresis including antibodies makes it possible to better separate antigen-antibody precipitation arcs and thus allows for an easier differentiation of the corresponding constituents. The procedure offers the advantage of allowing the combination of several other interesting techniques and makes possible a change of conditions between the first and the second electrophoresis. See abstract to Blanc.

One of ordinary skill in the art would have been motivated to employ the 2D antibody procedure taught by Blanc because Blanc taught that this was a method of interest in the study of complex protein mixtures, such as different biological fluids. See abstract.

Unla et al. in view of Blanc differ from the instant invention in not specifically teaching the use of an antibody array.

However, antibody arrays were taught in the prior art by Chu et al. Chu et al. teach that microarray based assays (antibody spot immunoarrays) are potentially capable of determining the amounts of hundreds of different analytes in a small sample. Arrays allow for the measurement of many different analytes simultaneously. See Chu et al. abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use antibody arrays as taught by Chu et al. in method of Unla et al. in view of Blanc because Chu et al. taught that microarray based assays (antibody spot immunoarrays) are potentially capable of determining the amounts of hundreds of different analytes in a small sample. Arrays allow for the measurement of many different analytes simultaneously. See Chu et al. abstract.

II. Claims 72-75, 77 and 80-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) in view of Bernard Blanc (Bulletin de la Societe de Chimie Biologique, 1959, Vol.41, 891-899, English Abstract) and further in view of Chu et al. (ACS Symposium Series, 1997, 657 (Immunochemical Technology for Environmental Applications, pages 170-184), Abstract Only as applied to claims 18, 71, and 88-92 above, and further in view of Ekins et al. (Clin Chem. 37/11, 1955-1967, 1991).

Please Unla et al. in view of Bernard Blanc and further in view of Chu et al. as set forth above.

Unla et al. in view of Bernard Blanc and further in view of Chu et al. differ from the instant invention in not specifically teaching multiple antigens and antibody preparations.

However, Ekins et al. teach method to detect proteins via multianalyte microspot immunoassays. An array of antibodies (device comprising multiple immobilized agents for protein detection such as antibodies) is exposed to proteins to monitor the expression and properties of a large number of proteins. See abstract and figures 4 and 5. The detection procedure can be evaluated with a radioactive isotopes (i.e.  $I^{125}$ ), an enzyme, chemiluminescent label, or fluorescence label. See page 1960. In one embodiment dual microspot assay devices are compared. See page 1961 figure 8 for example.



The microarrays taught by Ekins can measure tens, hundreds, or thousands of analytes. Thus the array may comprising 106 Ab (antibody) micro-spots each directed against a different analyte See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the protein patterning procedures as taught by Unla et al. in view of Bernard Blanc and further in view of Chu et al. with multiple antigens and antibodies as exemplified by Ekins et al. because Ekins et al. taught that antibody arrays can be configured to measure tens, hundreds, or thousands of analytes. See abstract.

Absent evidence to the contrary the adjustment of the prior art to employ multiple antigens and antibodies is deemed routine. It has been held that the provision of adjustability, where need, involves only routine skill in the art. In re Stevens, 101 USPQ 284 (CCPA 1954).

One of ordinary skill in the art would have been motivated to utilize multiple antigens and antibodies in order to generate more data sets for analysis.

III. Claims 76, 78-79 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unla et al. (Electrophoresis, 1997, 18, pages 2071-2077) in view of Bernard Blanc (Bulletin de la Societe de Chimie Biologique, 1959, Vol.41, 891-899, English Abstract) and further in view of Chu et al. (ACS Symposium Series, 1997, 657 (Immunochemical Technology for Environmental Applications, pages 170-184), Abstract Only as applied to claims 18, 71, and 88-92 above, and further in view of James F. Cupo (Journal of Chromatography, 569, 1991, 389-40).

Please Unla et al. in view of Bernard Blanc and further in view of Chu et al. as set forth above.

Unla et al. in view of Bernard Blanc and further in view of Chu et al. differ from instant invention in not teaching protein expression pattern evaluation in cancer diseases or virus cell lines (like T cells).

However, Cupo teaches a two-dimensional polyacrylamide gel electrophoresis procedure to measure matrix proteins. The proteins are tissue-type specific and can reflect changes in the state of differentiation of a cell. The method can further distinguish between a diseased cell and a normal cell. The disease states include various cancers, autoimmune disease, and adenoviral infection. See abstract.

The method is quick and efficient employing the appropriate antibodies to the protein of interest. Page 403, 1st paragraph. Protein patterning in T lymphocytes (T cells) is outlined on page 400.

The method is used to detect early stages of viral infection because a virus must replicate cellular components associated with the nuclear matrix. Such changes are evident in protein patterning analysis. See page 403 – 4.3.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use protein patterning procedures to evaluate cancer diseases or virus cell lines (like T cells) and further allowing for cellular replication distinctions (differential development) via polyacrylamide as taught by Cupo in the protein procedure of Unla et al. in view of Bernard Blanc and further in view of Chu et al. because Cupo taught that two-dimensional gels can determine tissue-type specific differences in nuclear matrix proteins and the differences between normal and carcinogenic cells. See page 402 - 4.2 Further these proteins play an important role in cells.

Utilization of the proteins can lead to the development of diagnostic agents to detect various diseased conditions of the cell and organism (including cancer and viruses). Cupo page 404.

### ***Response to Arguments***

6. Applicant's amendments and argument's filed 12/15/08 have been considered but were not found persuasive.

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In particular, applicant contends that the combination of Unlu, Blanc and Chu do not make the instant invention obvious because Unlu and Blanc are directed to electrophoresis procedures while Chu involves arrays. This argument was considered but not found persuasive because the prior art has demonstrated that electrophoresis procedures can be converted to microarray applications. This is supported by the reference to Elkins et al. (Clinical Chemistry, Vol.44, No.9, pages 2015-2030, 1998). Therefore the combination is not inoperable but merely teaches/makes obvious the conversion of electrophoresis to microarray applications.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., proteins that are mobile) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims do not require that the proteins are mobile/immobile.

Applicant contends that Elkins et al. and Cupo does not overcome the deficiencies of Unlu, Blanc and Chu. However, Unlu, Blanc and Chu have been considered a priori and are maintained. Accordingly, the dependent rejections are also maintained.

7. For reasons aforementioned, no claims are allowed.

**Remarks**

8. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Fields et al. (U.S. Patent #5,283,173) disclosed systems to measure protein-protein interactions.

9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week.

In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached on (571) 272-0806.

Any inquiry of a general nature or relating to the status of this application should be directed to Group TC 1600 whose telephone number is (571) 272-1600.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*Lisa V. Cook*  
*Remsen 3C-59*  
*(571) 272-0816*  
*12/20/08*

/Lisa V. Cook/  
Primary Examiner, Art Unit 1641